

REMARKS**Information Disclosure Statement**

An Information Disclosure Statement (IDS) was filed on May 25, 2001 and a Supplemental IDS was filed on March 17, 2003. The Examiner indicates that the original copies of the IDS and Supplemental IDS were found in the file wrapper of the application. As requested, Applicants are enclosing copies of the IDS and Supplemental IDS, along with copies of the cited references and a copy of the postcard receipts indicating the U.S. Patent & Trademark Office received all of these papers. Accordingly, Applicants understand that no fees are due and no certification under 37 C.F.R. 1.97(e) is required for entry and consideration of the cited references. Applicants respectfully request that the Examiner enter the IDS and Supplemental IDS in the record and return a copy of the initialed Form PTO-1449 with the next communication.

Rejection of Claims 1-3, 5-13 and 18-19 Under 35 U.S.C. § 103(a)

Claims 1-3, 5-13 and 18-19 remain rejected under 35 U.S.C. § 103(a) as being obvious over Earhart in view of McGall for the reasons set forth in the Office Action mailed May 28, 2003. The Examiner states that the hybridization intensities provided in the Declaration filed March 14, 2003 do not provide a direct correlation between reduction in iodine concentration and increase in hybridization signal intensity.

The rejection appears to be primarily based upon incorrect assumptions regarding the claimed invention. The Examiner has stated that the data presented in the Declaration do not demonstrate a direct correlation between reduction in iodine concentration and increase in hybridization signal intensity. Based on upon the teachings of the instant application, this statement is incorrect. One skilled in the art would not expect to see a direct correlation between iodine concentration and hybridization signal intensity. Instead, the teachings of the instant application would lead one skilled in the art to predict that there would be a concentration of iodine where hybridization signal intensity was maximized. This is due to the iodine apparently causing two or more chemical reactions in a nucleic acid array. The first reaction is the oxidation of a phosphite ester linkage to a phosphate ester linkage. The second (or further) reaction, which was not recognized in the art of record, involves iodine reacting with a nucleic acid array to reduce its functional performance. The maximum hybridization signal intensity occurs at the

point where the first reaction is maximized (*e.g.*, has gone to completion) and the second (or further) reaction is minimized (*e.g.*, has not occurred).

Prior to Applicants' invention, one would have expected a different result when using iodine to oxidize phosphite ester linkages. Previously, one skilled in the art would have simply expected a monotonic decrease in functional performance in a nucleic acid array as the iodine concentration decreased, due to incomplete oxidation of the array. In addition, one skilled in the art would have expected functional performance to reach an asymptote as iodine concentration increased, because functional performance would have been expected to remain essentially the same once complete oxidation of the phosphite ester linkages had occurred. Importantly, one skilled in the art would not have expected functional performance to decrease at higher iodine concentrations (*e.g.*, at 0.1 M).

Thus, contrary to the Examiner's statement, one skilled in the art would *not necessarily* expect the hybridization signal intensity for a nucleic acid array oxidized with 0.01 M iodine solution to have a greater signal intensity (*i.e.*, enhanced functional performance) than a nucleic acid array oxidized with a 0.02 M iodine solution based upon the teachings of the instant application. Instead, one skilled in the art would recognize that signal hybridization intensity would initially increase as iodine concentration was lowered from 0.1 M, would reach a maximum and then decrease as the iodine concentration was lowered further.

The claimed method is therefore unexpected in view of the art of record, because it provides a method of enhancing functional performance of a nucleic acid array by using a lesser concentration of iodine to oxidize phosphite ester linkages to phosphate ester linkages. There is no teaching or suggestion in the art of record that functional performance of a nucleic acid array would improve as the iodine concentration used for synthesis decreased. To the contrary, one skilled in the art would have expected that decreasing the iodine concentration would either fail to improve or diminish functional performance of the nucleic acid array.

The Examiner states that on page 5 of the Declaration, it is stated that the results presented are for illustrative purposes. The Examiner proceeds to question whether the data presented is truly representative of the claimed concentrations of iodine. The Examiner has taken the statements of the Declaration out of context and has failed to properly accord the Declaration the weight that it is entitled. The Declaration states, “[t]hese results are presented here for illustrative purposes, *but are representative of a large volume of data that has been generated as part of an extensive optimization of the oxidant reagent formulation.*” (Emphasis added.)

Thus, it is clear that the data in the Declaration are representative. The Examiner is reminded that the Declarant has attested that the statements made in the Declaration are true statements and has acknowledged the consequences of making willful false statements. The Examiner has cited no evidence as to why the statements made in the Declaration should be questioned. For this reason, the Examiner should accept the data as being representative of a larger body of data.

The Examiner also states that the hybridization intensities from nucleic acid arrays prepared using the claimed concentrations of iodine are not considered to be statistically different than the hybridization intensities of array preparing using a solution of about 0.1 M iodine. Applicants respectfully disagree. Taking the 0.1 M hybridization intensity as 100% in the two experiments presented in the Declaration, the mean results of the two experiments are as follows:

<u>Iodine Concentration</u>	<u>% Signal Intensity (\pm standard deviation)</u>
0.01 M	123.5 \pm 1.15%
0.02 M	160.7 \pm 5.7%
0.05 M	124.8 \pm 0.95%
0.10 M	100%

Thus, the hybridization signal intensities of nucleic acid arrays prepared with iodine concentrations of less than 0.10 M are all at least 3 standard deviations greater than the signal intensities of arrays prepared with 0.10 M iodine. A difference of 3 or more standard deviations is generally accepted to indicate that data reach the threshold of statistical significance. Moreover, Applicants maintain that the data provided in the Declaration can be extrapolated to encompass the entire claimed range.

The issue regarding the term “about” is addressed below in the rejection under 35 U.S.C. § 112, second paragraph. As discussed below, one skilled in the art can readily determine the scope of the instant claims.

In summary, the instant claims are non-obvious over the art of record. The invention is based upon the surprising discovery that the hybridization signal intensity of nucleic acid arrays can increase when the claimed concentrations of iodine are used, as opposed to using concentrations of 0.1 M or greater, which are disclosed in the art of record. Iodine apparently participates in two or more reactions with nucleic acid arrays, particularly at increased iodine

concentrations. At least one of these reactions is deleterious to the functional performance of the array. The deleterious effects of iodine on a nucleic acid array are not taught or otherwise suggested in the art of record. Thus, the instant claims are non-obvious over the art of record. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claim 18 Under 35 U.S.C. § 112, First Paragraph

Claim 18 is rejected under 35 U.S.C § 112, first paragraph, as failing to comply with the written description requirement. The Examiner states that the claims contain subject matter that was not described in the specification. The Examiner further states that it is unclear how the disclosure of 0.02 M would inherently disclose ranges that are two-fold less than 0.02 M.

As discussed below, the Examiner's consideration of Applicants' prior remarks fails to take into account the fact that the range of about 0.005 M to about 0.05 M was disclosed in the application as filed (see, for example, page 3, lines 11-14 and Claims 1-3). The Examiner appears to have focused only on the specifically disclosed value of 0.02 M and has not considered the full teachings of the disclosure.

Once again, Applicants refer to MPEP § 2163.05, which has a paragraph specifically devoted to ranges:

With respect to changing numerical range limitations, the analysis must take into account which ranges one skilled in the art would consider inherently supported by the discussion in the original disclosure. In the decision in *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976), the ranges described in the original specification included a range of "25%- 60%" and specific examples of "36%" and "50%." A corresponding new claim limitation to "at least 35%" did not meet the description requirement because the phrase "at least" had no upper limit and caused the claim to read literally on embodiments outside the "25% to 60%" range, however a limitation to "between 35% and 60%" did meet the description requirement.

In contrast, MPEP § 2163.06, to which the Examiner refers, does not specifically address range limitations in the context of the description requirement. As such, MPEP § 2163.05 is believed to be more relevant to the issue of written description with respect to Claim 18.

A more detailed reading of *in re Wertheim* finds that the CCPA was concerned with determining whether a broader range also describes a somewhat narrower range:

In the context of *this* invention, in light of the description of the invention as employing solids content within the range of 25-60% along with specific embodiments of 36% and 50%, we are of the opinion that, as a factual matter, persons skilled in the art would consider processes employing a 35-60% solids content range to be part of appellants' invention and would be led by the Swiss disclosure so to conclude. . . . The PTO has done nothing more than to argue lack of literal support, which is not enough.
(Emphasis original.) *Id.*

As noted above, the application as filed discloses the range of about 0.005 M to about 0.05 M iodine, both in the body of the specification and in the claims. Claim 18 is directed to a reaction mixture having about 0.01 M to about 0.05 M iodine. Consequently, the range of Claim 18 falls entirely within the range originally disclosed in the application.

Thus, the range recited in Claim 18 is analogous to the range that the CCPA found to meet the description requirement in *Wertheim*. In *Wertheim*, the specification disclosed a range of 25% to 60%. The CCPA found that a range of 35% to 60%, which fell within the disclosed range, met the description requirement. The range that the CCPA found to lack written description included values that fell outside of the originally disclosed range. Obviously, the range recited in ***Claim 18 does not include values that fall outside of the originally disclosed range.*** Moreover, the Examiner has not provided any reasoning as to why one skilled in the art would not recognize the range of Claim 18 to be part of Applicants' invention. It is improper to reject a subrange that is somewhat narrower than a disclosed range simply because the literal language for the subrange (*e.g.*, of Claim 18) does not literally appear in the specification. Based on the disclosure and because it is completely encompassed within the original disclosure, one skilled in the art would certainly consider a process using about 0.01 M to about 0.05 M iodine to be part of the invention.

For these reasons, Claim 18 fully complies with the description requirement. The range of about 0.01 M to about 0.05 M is inherently disclosed by the range of about 0.005 M to about 0.05 M that is found in the application as filed and one skilled in the art would immediately recognize this range to be part of the invention. Reconsideration and withdrawal of the rejection is requested.

Rejection of Claims 1-19 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-19 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter that applicant regards as the invention.

The Examiner states that there is nothing in the specification, prosecution or the prior art to provide any indication as to what range of specific activity is covered by the term "about".

Applicants respectfully disagree with Examiner's characterizations of *W.L. Gore & Associates* and the state of the art regarding determining iodine concentration. It is assumed that the Examiner is using the term "specific activity" as a synonym for iodine concentration. (Clarification is otherwise requested.) Much like determining a length of time with a stopwatch in *W.L. Gore & Associates*, determining concentrations of an element or a substance (or preparing a solution containing a particular concentration of a substance) is trivial to one of ordinary skill in the art and such analytical chemistry represents an extremely well-developed field. As such, one skilled in the art would readily be able to determine what concentrations are meant when a concentration is "about" a particular value. Because preparing solutions containing a particular concentration of a substance and determining concentrations is so well known in the art (particularly when the substance is iodine), there is no need for either the specification or the prosecution to provide additional disclosure on the meaning of "about" as it relates to the concentrations of iodine. This is analogous to *W.L. Gore & Associates*, because there is no indication in that case that either the specification or prosecution included a discussion on how to quantify time with a stopwatch. It is simply understood that measuring quantities such as time and concentrations are routine matters and would be known to one skilled in the art without having to refer to the specification or prosecution history. Thus, Applicants maintain that the instant claims present a situation analogous to that faced in *W.L. Gore & Associates*, where claims using the term "about" were found to be definite and meet the requirements of 35 U.S.C. § 112, second paragraph.

The Examiner also states that it is unclear as to which other concentrations of iodine would also possess the ability to oxidize a phosphite ester linkage to a phosphate ester linkage. It is clear from the specification and the prior art that a broad range of iodine concentrations are capable of oxidizing a phosphite ester linkage to a phosphate ester linkage. The present application discloses a method where oxidizing phosphite esters using an iodine concentration in the recited range has been found to yield nucleic acid arrays having unexpectedly improved functional performance. Nevertheless, many other iodine concentrations (including concentrations outside the disclosed ranges) can be used to oxidize phosphite esters.

Thus, the term "about", as used to describe iodine concentrations in the instant claims, is sufficiently clear to one skilled in the art. Preparing solutions containing particular

concentrations of iodine and determining the concentration of iodine are routine to one skilled in the art and can be carried out with relative precision. The Examiner has provided no evidence or reasoning to the contrary. As such, one skilled in the art could readily determine whether he or she is infringing the instant claims over their full scope. Thus, the instant claims are definite. Reconsideration and withdrawal of the rejection are respectfully requested.

Objection to Claim 4

Claim 4 is objected to as being dependent upon a rejected base claim. As discussed above, Applicants maintain that the base claim is allowable and thereby decline to rewrite Claim 4 as an independent claim. Withdrawal of the objection is requested upon allowance of the base claim.

Clarification of Status of Claims 4 and 14-17

Claims 14-17 are indicated as being allowed in the Office Action Summary and Claim 4 is indicated as being objected to, however, Claims 1-19 inclusive are rejected under 35 U.S.C. § 112, second paragraph. Clarification is requested as to the status of these claims.

CONCLUSION

In view of the above remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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